Remarks

Applicant's attorney thanks the Examiner for the helpful comments made during the personal interview held at the USPTO on August 28, 2003. Applicant submits herewith a response and amended claim set consistent with discussions that occurred during that interview.

Applicant noticed the filing date on this Office Action, Paper 18, is still incorrect. Applicant submitted a Notice of Error and a copy of the Filing Receipt on September 24, 2001, stating then that the filing date was incorrect. The correct filing date is September 22, 1999, and not October 21, 1999.

In this response, Applicant has amended claims 1, 11, and 12 and has cancelled claims 13- 15 without prejudice. Support for the claim amendments can be found throughout the specification and in particular on page 2, lines 15 and 16, page 3, line 28 to page 4, line 10, and page 4, line 27 to page 5 line 27.

In Applicant's response to the restriction requirement on March 20, 2001, Applicant submitted two new claims numbered 14 and 15. However, it does not appear that these amended claims were entered as they were not examined in this Office Action. Regardless, Applicant does not wish to pursue these claims at this time.

REJECTION UNDER 35 U.S.C. § 103

Claims 1-13 stand rejected under 35 U.S.C. § 103 as being unpatentable over Dietrich et al. (Moderate Hyperglycemia Worsens Acute Blood-Brain Barrier Injury After Forebrain Ischemia in Rats, *Stroke* 1993; 24:111-16) in view of Efendic et al. (WO 98/8531) or Efendic (WO98/08873). In addition, Claims 1-13 stand rejected over Dietrich et al. in view of Chen et al. (U.S. Patent 5,512,549). The Examiner relies on the Dietrich reference for the proposition that hyperglycemia is a risk factor for stroke and is associated with a worse prognosis. The Examiner cites the Efendic references and the Chen reference for the proposition that GLP-1 has insulinotropic properties and can normalize blood glucose levels in patients with hyperglycemia without risk of hypoglycemia. Based on these teachings, the Examiner asserts that it would have been obvious to use GLP-1 to reduce mortality and morbidity associated with stroke.

While one way to reduce risks associated with stroke may be to aggressively manage hyperglycemia as a result of diabetes before a stroke, Applicant's invention involves treating

patients after they have had a stroke. The Dietrich reference discusses only the consequences of pre-ischemic hyperglycemia, not post-ischemic metabolic changes. Applicant's invention focuses on a part of the disease that has been overlooked with respect to providing a treatment that will result in a reduced risk of morbidity or mortality.

To support a *prima facie* case of obviousness over a combination of prior art references, the Examiner must establish that the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Federal Circuit has also in several cases stated that hindsight is not a justifiable basis on which to find an invention obvious. *See In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999). To avoid a hindsight analysis wherein the inventor's teachings are used against him, "there must be a rigorous application of the requirement for showing the teaching or motivation to combine the prior art references." *Id.* at 999.

In this case, the cited references do not explicitly or implicitly teach, suggest, or motivate a skilled person to combine the references and arrive at the invention without using Applicant's specification. The Dietrich reference focuses on hyperglycemia *prior* to an ischemic event. As stated in the Dietrich reference, "The purpose of this study was to determine whether *preischemic* hyperglycemia exaggerates the BBB consequences of normothermic cerebral ischemia." (Dietrich et al., p. 112, emphasis added). The pre-clinical rat study discussed in the Dietrich reference involved artificially inducing hyperglycemia by administering a dextrose solution prior to inducing an ischemic event. The Dietrich reference concluded that moderate *hyper*glycemia aggravated blood brain barrier breakdown. However, the Dietrich reference also noted that "*hypo*glycemia may potentially worsen ischemic brain injury by increasing cerebrovascular permeability." (Dietrich et al., p. 114, emphasis added).

The Dietrich reference does not discuss treatment of any kind and actually teaches away from using an insulinotropic agent post-stroke by suggesting that lower glucose levels may potentially worsen brain injury caused by a stroke. The Dietrich reference also does not even mention any potential post-stroke metabolic changes that would be targets for treatment. Further, there are additional reports in the literature that either suggest no correlation between hyperglycemia and poor prognosis after suffering a stroke or suggest glucose may actually protect the brain from ischemic neuronal damage. (*See* Tracey et al. Hyperglycaemia and

mortality from acute stroke. *Q. J. Med.* 1993; 86:439-446; Woo et al. The Influence of Hyperglycemia and Diabetes Mellitus on Immediate and 3-Month Morbidity and Mortality After Acute Stroke. *Arch Neurol.* 1990; 47:1174-77; and Zasslow et al. Hyperglycemia Decreases Acute Neuronal Ischemic Changes After Middle Cerebral Artery Occlusion in Cats. *Stroke* 1989; 20:519-523).

The methods claimed in the amended claim set submitted with this response require that the GLP-1 compound be administered after a patient has suffered a stroke. Further, the methods of the claimed invention are useful regardless of the condition of the patient prior to having the stroke. Thus, the invention is useful in treating both diabetics as well as non-diabetics that have suffered a stroke.

In addition, more data has been generated further supporting the claimed invention. The data clearly suggest a clinical benefit from administering a GLP-1 compound to stroke patients. A study looking at potential neurological deficits due to brain-damaged areas involved in the regulation of sensori-motor functions as measured by disturbances of fore and hind limb movements in both diabetic Goto-Kakizaki (G-K) rats and non-diabetic Wistar rats has been performed. The rats were first trained to walk across a beam to establish a baseline. Then, both sets of rats were subjected to an insult of focal brain ischemia by short lasting compressions of a specific area in the sensori-motor cortex. Next, the rats were tested 24 hours after insult for their ability to traverse the beam. The beam walking tests were repeated every 24 hours for up to 14 days in some experiments.

In the control groups, both the diabetic and non-diabetic rats demonstrated markedly impaired beam walking ability following the brain insult. In the treated groups, both sets of rats were administered a GLP-1 compound by intravenous infusion along with the brain insult. The GLP-1 compound treated non-diabetic Wistar rats were able to regain their ability to walk across the beam three days after brain insult compared to greater than 6 days for the untreated group. The GLP-1 compound treated diabetic G-K rats were able to regain their ability to walk across the beam five days after brain insult compared to greater than 8 days for the untreated group.

In summary, Applicant's invention provides a benefit to stroke patients after they have had a stroke. This part of the disease has been overlooked with respect to providing a treatment that will result in a reduced risk of morbidity or mortality. The primary reference cited by the Examiner focuses on whether preischemic hyperglycemia aggravates blood brain

barrier breakdown and does not mention, yet alone correlate, any post-ischemic metabolic changes with stroke prognosis. There is no teaching, suggestion, or motivation to combine the references and arrive at the use a GLP-1 compound to treat these post-ischemic metabolic changes without using Applicant's specification.

Summary and Conclusion

Applicant respectfully asserts that the Examiner's obviousness rejection has been overcome and that the application is now in condition for allowance. If, for any reason, the Examiner feels that a telephone conversation would be helpful in expediting the prosecution of this case, the Examiner is urged to call me.

Respectfully submitted,

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